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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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GIBBS, TERRA C

ART UNIT	PAPER NUMBER
1635	9

DATE MAILED: 04/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,265	BACHY ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 19-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 19-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's Preliminary Amendment, filed December March 22, 2002 in Paper No. 8 is acknowledged. Claims 15-18 have been canceled. New claims 20 and 21 have been added.

Claims 1-14 and 19-21 are pending in the instant application.

Nucleotide and/or Amino Acid Sequence Disclosure

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR §1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 §1.821 through 1.825 for the reason(s) set forth below. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 Fed. Reg. 18230, May 1, 1990. It is noted that the application fails to comply with 37 CFR §1.821(a) and (d).

37 CFR §1.821(d) states, "Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application".

For example, page 3, line 32, page 8, line 16, page 12, line 3 and claim 8 disclose sequences which do not disclose the use of the sequence identifier, preceded by "SEQ ID NO:" as described in 37 CFR §1.821(d). The above are examples and are not intended to indicate that the Examiner has made an exhaustive review of the application. Applicant must fully comply with the sequence rules for any response to this action to be considered fully responsive.

Specification

The Specification is objected to for the following informalities: Pages 4-5 makes reference to Figures 1-11. However, the specification as filed contains no such Figures 1-11. Correction is required. It is noted that references to Figures 1-11 may appear elsewhere in the Specification.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 19 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19, 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 provides for an immunization composition for human use, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 6 recites, "the oligonucleotide as claimed in either of claims 4 or 5, wherein the repeated 5' TTN_1N_2TT 3' units are separated by a nucleotide N_3 which is identical or different from other N_3 nucleotides and which is A, C, T, or G". Claim 7 recites, "the oligonucleotide as claimed in claim 6, wherein the 5'-most nucleotide N_3 is cytosine".

Claims 6 and 7 are indefinite because they rely on claim 5, wherein the repeated 5' TTN_1N_2TT 3' units are separated by a nucleotide N_3 which is identical or different from other N3 nucleotides and which is A, C, T, or G. In claim 5, the 5' TTN_1N_2TT 3' unit is repeated only twice. Therefore, there is only (1) N_3 nucleotide and thus, *other* N_3 nucleotides do not exist.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 20 and 21 are drawn to a method of stimulating an immune response in a human or enhancing an immune response to an antigen in a human by administering an immunostimulant oligonucleotide.

The instant invention specification provides methodologies for stimulating lymphocyte proliferation, induction of CD86 and CD25 expression in B lymphocytes and induction of IL-10 and interferon-γ secretion in cell culture (*in vitro*) using immunostimulatory oligonucleotides (see Examples 1-7).

Parronchi et al. (Journal of Immunology, 1999 Vol. 163:5946-5953) assert that the nature of immunostimulatory sequences active in humans remains unclear (see page 5952, last paragraph).

Singh et al. (Nature Biotechnology, 1999 Vol. 17:1075-1081) assert that immunostimulatory oligonucleotides have mainly been evaluated only in rodent models and with murine cells; thus, their potency and safety in humans remains to be established (see page 1077, second column).

The assertions of Parronchi et al. and Singh et al. indicate that further research is required in the art to understand the nature and safety of immunostimulatory oligonucleotides in humans.

Furthermore, the unpredictability of the art of nucleic acid therapy in general adds to the lack of enablement for the current invention. For example, Branch (TIBS, February 1998 Vol. 23, pages 45-50) addresses the unpredictability and the problems faced in the antisense art with the following statements: "Antisense molecules and ribozymes capture the imagination with

their promise or rational drug design and exquisite specificity. However, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "To minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. This is a challenging quest."; "However, their unpredictability confounds research application of nucleic acid reagents."; "Non-antisense effects are not the only impediments to rational antisense drug design. The internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,..."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "Because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. Antisense compounds are no exception. As is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "Because it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "Binding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. Since accessibility cannot be predicted, rational design of antisense molecules in not possible."; and, "The relationship

between accessibility to oligonucleotide (ODN) binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored...It is not yet clear whether *in vitro* screening techniques...will identify ODN's that are effective *in vivo*."

Jen et al. (Stem Cells, 2000, Vol. 18:307-319) discuss antisense-based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al. discuss the advances made in the art but also indicate that more progress needs to be made in the art. In the conclusion of their review, Jen et al. assert, "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated, "The key challenges to this field have been outlined above. It is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. A large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al. that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

Dias et al. (European Journal of Pharmaceutics and Biopharmaceutics, 2002 Vol. 54:263-269) addresses the limitations of antisense-based therapy. Dias et al. state, "Even though the antisense strategy is widely employed currently, it has certain defined limitations. Although it is relatively easy to synthesize phosphodiester oligonucleotides, these cannot *[emphasis added]* be used as drugs due to their propensity to be easily degraded by cellular nucleases" (see page 263, first column). Dias et al. further discuss that different methods, such as electroporation, microinjection or the binding to particular peptides with membrane translocation properties have

been developed to overcome internalization problems, however these methods are easily applied in cultured cells, but may or may not be useful in *in vivo* systems (see page 263, second column).

In view of the unpredictability in the art, the specification as filed does not provide adequate guidance or examples that would show by correlation how one skilled in the art would practice the claimed invention without having to engage in trial and error or undue experimentation. The specification as filed contemplates a method of stimulating an immune response or enhancing an immune response to an antigen in a human by administering an immunostimulant oligonucleotide. However, it is unclear how the specific cell culture (*in vitro*) data is correlated with/or representative of a method of stimulating an immune response or enhancing an immune response to an antigen in a human by administering an immunostimulant oligonucleotide. It is also unclear how any immunostimulant oligonucleotide will stimulate an immune response or enhance an immune response to an antigen in a human where no specific guidance (i.e. specific mode of treatment, delivery route, tissue specificity, etc.) is provided.

The specification does not provide particular guidance or particular direction for a method of stimulating an immune response or enhancing an immune response to an antigen in a human by administering an immunostimulant oligonucleotide. The specification does not provide guidance for the delivery of immunostimulant oligonucleotides into the target organ and target cells in a human in quantity sufficient to stimulate an immune response or enhance an immune response to an antigen in a human. While the specification provides guidance for stimulating lymphocyte proliferation, inducing CD86 and CD25 expression in B lymphocytes and inducing IL10 and γ interferon secretion in cell culture using immunostimulatory oligonucleotides, the specification provides no particular nexus between a method of stimulating

an immune response or enhancing an immune response to an antigen in a human by administering an immunostimulant oligonucleotide, as contemplated by the specification. The specification provides no particular guidance of direction for addressing the problems of targeting permanence, immunogenicity, etc, for nucleic acid delivery in a human. The specification provides no particular guidance or direction for a method of stimulating an immune response or enhancing an immune response to an antigen in a human using the immunostimulant oligonucleotides of the claimed invention. Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use the claimed invention. Due to the lack of specific guidance in the specification as filed and the lack of correlation between stimulating lymphocyte proliferation, inducing CD86 and CD25 expression in B lymphocytes and inducing IL10 and γ interferon secretion in cell culture (*in vitro*) and a method of stimulating an immune response or enhancing an immune response to an antigen in a human by administering an immunostimulant oligonucleotide, one of skill in the art would require specific guidance to practice the current invention. The current specification does not provide such guidance to a method of stimulating an immune response or enhancing an immune response to an antigen in a human by administering an immunostimulant oligonucleotide and one of skill in the art would be required to perform trial and error or undue experimentation. The quantity of experimentation required to practice the invention would include the de novo determination of how to engineer and deliver an immunostimulatory oligonucleotide such that a an immune response or enhanced immune response to an antigen in a human would occur, particularly, in view of the obstacles

needed to overcome to use nucleic acid therapies as exemplified in the references discussed above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 9, 10 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Hutcherson et al. [WO 95/26204].

Claims 1, 2, 9 and 10 are drawn to an immunostimulant oligonucleotide comprising the formula 5' $TTN_1 N_2TT$ 3', wherein the oligonucleotide comprises from 6 to 100 nucleotides, wherein the oligonucleotide induces lymphocyte proliferation and cytokine secretion. Claim 19 is drawn to an immunization composition comprising the at least one immunization antigen and at least one immunostimulatory oligonucleotide comprising the formula 5' $TTN_1 N_2TT$ 3'.

Hutcherson et al. ('204) disclose methods of stimulating a local immune response in selected cells or tissues employing immunopotentiating oligonucleotides (see Abstract). Hutcherson et al. ('204) also disclose an immunostimulant oligonucleotide comprising the formula 5' $TTN_1 N_2TT$ 3' (see SEQ ID NO:1). Hutcherson et al. ('204) further disclose that SEQ ID NO :1 induced lymphocyte proliferation (see page 18, lines 29-37 and page 19, lines 1-9) and cytokine secretion (see page 18, lines 7-15). Hutcherson et al. ('204) further disclose that

oligonucleotides of the invention may be modified to enhance antiviral activity through stimulating local immune responses (see page 14, lines 18-22).

Therefore, Hutcherson et al. ('204) anticipate the instant invention.

Claims 1, 2, 9, 10 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Parronchi et al. (Journal of Immunology, 1999 Vol. 163:5946-5953).

Claims 1, 2, 9 and 10 are described above (see page 9). Claim 12 is dependent on claim 1 and includes all the limitations of claim 1, wherein the immunostimulatory oligonucleotide induces γ interferon secretion.

Parronchi et al. disclose phosphorothioate oligodeoxynucleotides promote the *in vitro* development of human allergen-specific $DN4^+$ T cells into Th1 effectors (see Abstract). Parronchi et al. also disclose an immunostimulant oligonucleotide comprising the formula 5' $TTN_1\ N_2TT$ 3' (see page 5947, Table 1: oligonucleotide 2105). Parronchi et al. further disclose that oligonucleotide 2105 induced interferon γ secretion (see Table III).

Therefore Parronchi et al. anticipate the instant invention.

Claims 1-8, 9, 13, 14 and 19 rejected under 35 U.S.C. 102(b) as being anticipated by Liang et al. (Journal of Clinical Investigation, 1996 Vol. 98:1119-1129).

Claims 1, 2, 9 and 19 are described above (see page 9). Claim 3 is dependent on claim 1 and includes all the limitations of claim 1, wherein N_1 represents adenine and N_2 represents guanine. Claim 4 is dependent on claim 1 and includes all the limitations of claim 1, wherein the formula 5' $TTN_1\ N_2TT$ 3' is repeated at least once. Claim 5 is dependent on claim 4 and includes

all the limitations of claim 4, wherein the formula 5' $TTN_1 N_2TT$ 3' is repeated at least twice. Claim 6 is dependent on claim 4 and includes all the limitations of claim 4, wherein the repeated formula 5' $TTN_1 N_2TT$ 3' units are separated by a nucleotide N_3 which is identical or different from other N_3 nucleotides which is A, C, T, or G. Claim 7 is dependent on claim 6 and includes all the limitations of claim 6; wherein the 5'-most nucleotide N_3 is cytosine. Claims 8 is dependent of claim 1 and includes all the limitations of claim 1, comprising the sequence 5' $TTAGTTCTTAGTTN_3TTAGTT$ 3'. Claims 13 and 14 are dependent on claim 1 and include all the limitations of claim 1, wherein the immunostimulatory oligonucleotide increases the expression of the activation marker CD 86 and cytokine receptor CD25 in human B lymphocytes.

Liang et al. disclose activation of human B cells by phosphorothioate oligodeoxynucleotides (see Abstract and Figure 2). Liang et al. also disclose an immunostimulant oligonucleotide comprising the formula 5' $TTN_1 N_2TT$ 3', wherein N_1 represents adenine and N_2 represents guanine (see page 1122, Figure 2, oligonucleotides 2105 and DSP19) as recited in claims 1, 2, and 3 of the instant invention, wherein the formula 5' $TTN_1 N_2TT$ 3' is repeated at least once; wherein the formula 5' $TTN_1 N_2TT$ 3' is repeated twice; wherein the repeated formula 5' $TTN_1 N_2TT$ 3' units are separated by a nucleotide N_3 which is identical or different from other N_3 nucleotides which is A, C, T, or G (see page 1120, Table 1: oligonucleotides DSP28, DSP39, DSP40 and DSP19) as recited in claims 4, 5 and 6 of the instant invention. Liang et al. also disclose an immunostimulant oligonucleotide wherein the 5'-most nucleotide N_3 is cytosine and comprises the sequence 5' $TTAGTTCTTAGTTN_3TTAGTT$ 3' (see page 1120, Table 1: oligonucleotide DSP19) as recited in claims 7 and 8 of the instant

invention. Liang et al. further disclose that oligonucleotide 2105 induced increased expression of the activation marker CD 86 and cytokine receptor CD25 in human B lymphocytes (see Figure 4) as recited in claims 9, 13, and 14 of the instant invention. Liang et al. further disclose that stimulatory motifs are important in the development of DNA-based vaccines (see page 1129, last paragraph) as recited in claim 19 of the instant invention.

Therefore, Liang et al. anticipate the instant invention.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Lang et al. (European Journal of Immunology, 1999 Vol. 29:3496-3506).

Claims 1 and 2 are described above (see page 9). Claim 3 is dependent on claim 1 and includes all the limitations of claim 1, wherein N_1 represents adenine and N_2 represents guanine.

Lang et al. disclose guanosine-rich oligodeoxynucleotides induce proliferation of macrophage progenitors in cultures of murine bone marrow cells (see Abstract). Lang et al. also disclose an immunostimulant oligonucleotide comprising the formula 5' TTN_1 N_2TT 3', wherein N_1 represents adenine and N_2 represents guanine (see page 3501, Table 2: oligonucleotide GR1BC).

Therefore, Lang et al. anticipate the instant invention.

Conclusion

Claims 1-14 and 19-21 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-8693 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
April 17, 2003

Ram R. Shukla

RAM R. SHUKLA, PH.D
PATENT EXAMINER